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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/896,802	07/18/97	RUSSEK	~~0146-2003~~

EXAMINER		ART UNIT	PAPER NUMBER
FREEDMAN, J			16

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KEVIN M. FARRELL
P.O. BOX 999
YORK HARBOR ME 03911

DATE MAILED:

04/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/896,802	Russek et al
Examiner	**Group Art Unit**
Jeffrey Fredman	1655

☒ Responsive to communication(s) filed on *Dec 30, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-11 and 15-18* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-11 and 15-18* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Continued Prosecution Application

1. The request filed on December 30, 1999, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/896,802 is acceptable and a CPA has been established. An action on the CPA follows.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 2, 5-11, 15, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Turnbow et al (Biotechniques (1993) 15(2):267-270) in view of Holmstrom et

al (Anal. Biochem. (1993) 209:278-283) and further in view of Parkhurst et al (Biochemistry (January 1995) 34:282-292).

Turnbow teaches a method of detection of a particular RNA sequence comprising: a) mixing a sample containing ribonucleic acids with an RNA probe have a sequence complementary to the sequence to be detected, said probe having a detectable label which is an indirect biotin label then bound to a chemiluminescent label which was attached within the probe, and incubating the mixture containing the sample and probe under conditions wherein complementary single stranded nucleic acids hybridizae and furhter wherein substantially all unhybridized single stranded nucleic acids are hydrolytically digested by RNAse (page 267, column 2 to page 268, column 1).

Turnbow does not teach the capture of the hybridized complex and detection thereon, nor does Turnbow teach the use of two fluorescent labels attached at the ends for fluorescent quenching where a first label is attached to a first base and a second label is attached to a second base.

Holmstrom teaches a method for detection of a particular nucleic acid sequence comprising: a) PCR amplification with a biotin labeled primer and a digoxigenin nucleotide to form a single strand which is double labeled with biotin and digoxigenin (page 278, column 2 to page 279, column 1), b) subsequent to the enzymatic reaction, contacting the mixture with a magnetic dynabead support coated with avidin such that specific binding pairs form between the biotin on the primer and the avidin atached to the support, the speciifc binding pairs being couple to the support (page 279, column 1), c) separating the support and binding pairs couple thereto

from the mixture and determing the detectable label coupled to the support the amoutn of detectable label coupled to the support being proportional to the amount of nucleic acid having the particular sequence to be detected which was present in the sample (page 279, column 1 to page 279, column 2 and page 281, table 1).

Parkhurst (Biochemistry) teaches a single stranded DNA probe labeled at a first 3' base and at a second 5' base with fluorescein and rhodamine respectively which probe is complementary to the target nucleic acid, said probe nucleic acid is shown and stated to alternate between a folded and unfolded configuration (page 285, abstract and page 292, column 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the RNAse protection method of Turnbow with the capture method of Holmstrom and the fluorescent labels of Parkhurst since Holmstrom states "In this report we describe a novel nonradioactive detection system which is rapid as well as sensitive. The handling is easy as it can be carried out in microtiter plates; furthermore, it is easily adapted to other primer sets (page 282, column 1)". An ordinary practitioner would have been motivated to use the capture method of Holmstrom, in which nucleic acid hybridizations were captured with biotin streptavidin linked magnetic beads or microtiter dishes for the advantages expressly noted by Holmstrom including rapid speed, ease of handling and highly sensitive detection. An ordinary practitioner would have been motivated to combine the fluorescent labels of Parkhurst with the RNAse protection and capture method of Turnbow in view of Holmstrom since Parkhurst states "The double-labeled oligomer is very effective in signaling hybridization (page 292, column 1,

paragraph 2)". Parkhurst further notes "Because of this exquisite sensitivity, ^{R*}oligo^{*F} may prove to be a very useful tool for investigating the physical behavior of oligomers in solution (page 292, column 2)". An ordinary practitioner would have been motivated to combine the fluorescent labels and FRET technique of Parkhurst with the method of Turnbow in view of Holmstrom for the express advantages of exquisite sensitivity and effectiveness in signaling hybridization as expressly noted by Parkhurst.

4. Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Turnbow in view of Holmstrom and further in view of Parkhurst and further in view of Thompson et al (J. Biol Chem. (1992) 267:5921-5926) and further in view of Mayrand.

Turnbow in view of Holmstrom and further in view of Parkhurst teach the limitations of claim 1 as discussed above. Turnbow in view of Holmstrom and further in view of Parkhurst do not teach S1 nuclease detection nor the use of multiple detections.

Thompson teaches a method of detection of a particular RNA sequence comprising: a) mixing a sample containing ribonucleic acids with an DNA probe have a sequence complementary to the sequence to be detected, said probe having a detectable label which is radioactive ^{32}P label, and incubating the mixture containing the sample and probe under conditions wherein complementary single stranded nucleic acids hybridizae and further wherein substantially all unhybridized single stranded nucleic acids are hydrolytically digested by S1 nuclease (page 5921 to page 5922). Thompson further teaches multiple detections (abstract and page 5921, column 2).

Mayrand teaches multiple different fluorescent labels (column 8, lines 21-45).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the protection method of Turnbow in view of Holmstrom and further in view of Parkhurst with the S1 nuclease protection assay of Thompson since Thompson states "We have adapted the S1 nuclease protection assay to measure multiple RNA species in a single sample by using synthetic antisense oligonucleotides of different lengths that are complementary to different RNA species (page 5921, column 2)". An ordinary practitioner would have been motivated to combine the methods in order to be able to perform multiple detections. Further, given the disclosure by Turnbow of nonradioactive labeling and given the disclosure by Mayrand of multiple different fluorescent labels, an ordinary practitioner would have been motivated to utilize multiple different fluorescent labels in order to avoid the use of radioactivity, permit sensitive fluorescent detection of the oligonucleotides, and permit capture and analysis by the method of Holmstrom since multiple labels could be individually detected by fluorimetry.

5. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Turnbow in view of Holmstrom and further in view of Parkhurst and further in view of Dower et al (U.S. Patent 5,639,603).

Turnbow in view of Holmstrom and further in view of Parkhurst teach the method of RNAse protection as discussed above for detection of nucleic acids. Turnbow in view of Holmstrom and further in view of Parkhurst do not teach the instance where the oligonucleotide is conjugated to an antibody to permit detection of the antibody antigen complex.

Dower teaches a method whereby antibody antigen complexes are identified by DNA tags (column 47, lines 8-37 and columns 18-22, especially column 19, line 47-60).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the protection method of Turnbow in view of Holmstrom and further in view of Parkhurst with the oligonucleotide tags and antibody-antigen detection method of Dower for the advantages recited above regarding the protection method and since Dower states "For instance, once could read the tage directly from the bead by sequencing or hybridization (column 19, lines 47-48)". This express teaching motivates the use of hybridization detection methods such as the RNAse or S1 nuclease protection methods disclosed above. Advantages of the method include ease of use and high sensitivity as discussed above.

Response to Arguments

6. Applicant's arguments filed December 21, 1998 have been fully considered but they are not persuasive.

Applicant argues that the invention improves upon the prior art since detection of partial hybridization is eliminated, thereby eliminating the requirement for gel electrophoresis. This argument is not found persuasive for several reasons. First, this argument assumes that incomplete digestion is a problem which is solved by the claimed invention. There are no limitations in the claims, nor evidence of a comparison in the specification between the invention and the prior art, which support the idea that this invention teaches elimination of partial hybridization. In order for this argument to be persuasive, evidence supporting such an assertion

combined with a limitation in the claims incorporating this result would be necessary. Second, the evidence of the prior art Turnbow reference demonstrates that complete digestion can be performed under appropriate conditions (page 268, figure 1, lane 5) where a single band from the B-actin probe as protected without a larger band is seen. An ordinary artisan is completely capable of routine optimization to reduce background.

Applicant then argues that the sensitivity of the Holmstrom method is due to PCR and that the sensitivity and effectiveness of the Parkhurst reference is drawn to a different application than that claimed. With regard to the Holmstrom reference, Holmstrom provides a variety of motivations besides sensitivity, including ease of use and rapidity of use. Any of these motivations would be sufficient for the ordinary practitioner to combine this method with that of Turnbow. With regard to the Parkhurst reference, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, an ordinary practitioner would have been motivated to substitute a known, and "exquisitely sensitive" type of label as taught by Parkhurst for other labels in order to utilize a non-radioactive label. As noted in MPEP 2144.06 " In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. In re Ruff , 256 F.2d 590, 118 USPQ 340 (CCPA 1958)".

Here, the prior art clearly recognizes the equivalence of a variety of different labeling techniques, ranging from the FRET technique of Parkhurst, to radioactive labels, to fluorescent labels, to fluorescent quenching, to enzymatic labels such as beta-galactosidase. Given specific motivation to utilize FRET for it's sensitivity and the equivalence with other labeling methods, an ordinary practitioner would have been motivated to use the Parkhurst labels.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeff Fredman, Ph.D. whose telephone number is (703) 308-6568.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Group 1800 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1655

April 25, 2000